UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,348	11/14/2003	Suheir Assady	85189-5400	4072

28765 7590 01/25/2005

WINSTON & STRAWN
PATENT DEPARTMENT
1400 L STREET, N.W.
WASHINGTON, DC 20005-3502

EXAMINER	
LIETO, LOUIS D	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,348	ASSADY ET AL.	
	Examiner	Art Unit	
	Louis D Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *20-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the Restriction was received on 12/14/2004. Claims 1-34 are pending in the instant application. Claims 20-25 are canceled. Applicants elected the subject matter of group I, original and amended claims 1-19, and insulin as the species of gene expressed by the insulin producing cells, with traverse. Original and amended claims 26 and 27 are withdrawn by the examiner from further consideration pursuant to 37 CFR 1.142(b). New claim 34 has been added and is considered to fall within the invention of group I. Claims 1-19 and 28-34 are currently under examination. Applicant is reminded that the claims have only been examined to the extent that they read on the elected subject matter. An action on the merits follows.

Election with Traverse

Applicant's election with traverse of the subject matter of group I, to a cell population comprising insulin-producing cells derived from human embryonic stem cells, and insulin as the species of gene expressed by the insulin producing cells in the reply filed on 12/14/2004 is acknowledged. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the grounds of restriction for reasons of record as discussed below.

Applicant argues that all the species in the application should be examined together since they are related in that they can be expressed by the glucose responsive insulin-producing cells of the present invention. Further, applicant argues that all the species are β-cell related genes that

can be expressed by present glucose responsive insulin-producing cells. While applicant's statements are acknowledged to be true they are not found persuasive in overcoming the grounds for an election of species of gene expressed by the insulin producing cells.

The species of genes are patentably distinct from each other because: 1) the genetic sequence of each gene differs from the others; 2) each gene encodes a specific protein that differs in structure and function from the others; and 3) the class of functions of the encoded proteins are quite different from each other. For example, insulin is a secreted protein that has systemic effects and is involved on glucose regulation, while IPF1/PDX1 and NgN3 are transcription factors that are active primarily in the pancreas and function by binding to DNA and regulating gene expression. Further, the Glut-2 glucose transporter and glucokinase genes are known to play a role in regulating feeding behavior and are expressed in cells other than β-cells, such as tissues within the brain (Roncero et al. (2004) J. of Neurochemistry. 88:1203-1210). Given the differences in structure, function and tissue expression profile the election of species is still deemed proper.

Applicant argues that elected group I encompasses the method claims 26-33 and that they should be rejoined and examined together. After a telephone interview with Allan Fanucci on 1/10/2005, the examiner offered to rejoin claims 28-33 and the applicant agreed.

The requirement is deemed proper and is therefore made FINAL.

Priority

Acknowledgement of applicants claim of priority to PCT/IL02/00369, filed on 5/14/2002, which claims benefit of provisional US Application No: 60/328,798, filed on 10/15/2001 and

Israel Application No: 05/15/2001, is acknowledged. However, An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). Specifically, applicant must include a reference to PCT/IL02/00369 and provisional US Application No: 60/328,798 in the beginning of the specification. Further, applicant should note that per current practice by the Office the 1 year bar of 35 U.S.C. 102(b) dates from the U.S. filing date and not from the foreign filing date. See MPEP 201.13:

> III. < **EFFECT OF RIGHT OF PRIORITY**
>
> The right to rely on the foreign filing extends to overcoming the effects of intervening references or uses, but there are certain restrictions. For example, the 1 year bar of 35 U.S.C. 102(b) dates from the U.S. filing date and not from the foreign filing date; thus if an invention was described in a printed publication, or was in public use in this country, in November 1981, a foreign application filed in January 1982, and a U.S. application filed in December 1982, granting a patent on the U.S. application is barred by the printed publication or public use occurring more than one year prior to its actual filing in the United States.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 7 and 8 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 1 reads on a cell population comprising insulin-producing cells derived from human embryonic stem cells (ESCs). Said cell population does not require the intervention of the hand-of-man and therefore encompasses a human pancreas, which

contains insulin producing β-islet cells and is derived from human ESCs, *in situ*. See MPEP 210.5. Claim 7 reads on a cell population comprising regulatable o insulin producing cells derived form human ESCs; and claim 8 reads where the regulation is due to glucose responsiveness. The β-islet cells of a human pancreas produce insulin in response to increased blood glucose levels. The claims are rejected since the broadest reasonable interpretation of the claims encompasses a human pancreas, within a human being.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not teach the existence of insulin producing cells derived from human ESCs over expressing hTERT. The art of record at the time of filing does not indicate that any hTERT over expressing human ESC cell lines capable of differentiating into insulin producing cells were available. The specification indicates that the reason for deriving a cell population comprising insulin-producing cells from hTERT overexpressing human ESCs is to overcome problems with enrichment and propagation of β-cells derived from normal human ESCs (Specification pg 26, Ex. 4). However, Halverson et al. teaches that transduction of human

β-cells with hTERT was not sufficient to prevent growth arrest after 10-15 cell divisions, which was similar to untransduced β-cells {Halverson et al. (2000) J. of Endocrinology. 166:103-109; pg 107, col. 1}. Halverson et al. indicates that senescence in some cell types, such as β-islets and human keratinocytes, may be driven by factors other than telomerase shortening (pg. 108, col. 1, pgph 2). Therefore, the art teaches that it is unpredictable that human ESCs that over express hTERT can be used to derive insulin-producing cells with decreased senescence.

The sole prospective working example (Ex 4A) that contemplates the use of human ESCs over expressing hTERT does not teach the existence of said cells, or the existence or use of any specific expression vector encoding hTERT. The specification does not provide any information on whether the hTERT coding sequence is stably expressed or integrated into a human ESC. In fact the specification does not provide any information on the use of any specific vector, or the vector's structure, sequence or method of construction. Some vectors, such as MLV, can have unpredictable results due to random integration. Yee et al. teaches that using the MLV vector to introduce genes into cells can lead to problems because MLV's random integration into the host genome can result in silencing or position effect in gene expression {Yee et al. (2001) Somatic Cell Mol Gent 26:159-74; Abstract}. Therefore, without guidance in the specification or in the art on the stable expression of hTERT in a human embryonic stem cell line, the skilled practitioner would be unable to predict how to practice the invention. Given the complete lack of enablement on how to manufacture insulin producing cells from human ESCs that over express hTERT, the art taught unpredictability of using some vectors to express a coding sequence within a cell, the lack of working examples using hTERT human ESCs and the

art taught inability of hTERT over expression to prevent senescence in β-cells, a skilled practitioner in the art would be unable to practice the invention as conceived.

Claims 28-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to enable a method of cell replacement therapy, comprising administering insulin producing cells to a subject in need. The sole working example (Ex. 5C) describes the xenogeneic engraftment of undifferentiated cells from stable human ESC clones into a nude mouse. The specification does not disclose that these cells can produce insulin. Soria et al. teaches that xenotransplantation of β-cells has multiple problems, such as the high costs, technical difficulty and immunological rejection {Soria et al. (2000) Diabetes 49:1-6; pg. 1, col. 1, pgph 2}. The specification does not describe the allogeneic engraftment of any human ESC derived insulin producing cells into a human. The working example does not teach that nude mouse have experimentally induced diabetes or any other problems with their pancreas. Further, while the example describes that teratomas were generated in the mice from the transplanted undifferentiated human ESC clones, no information on the production of insulin by these clones is reported. Finally, the introduction of germ cell tumors as a result of engraftment of human ESC clones is not recognized in the art as a form of cell replacement therapy or a method of treatment of a subject in need. Given the total lack of enablement in the specification for a method of cell replacement therapy comprising administering human ESC derived insulin

producing cells to a patient in need, and the art taught problems of xenotransplantation of β-cells, a practitioner skilled in the art would be unable to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, 6, 8, 12, 13, 14, 15, 16, 28, 30, 31, 33, and 34 are rejected under 35 U.S.C. 102(a) as being anticipated by Lumelsky et al. {Lumelsky et al. (April 26, 2001) Science 292:1389-1394}. Applicant should note that the date of public availability of this article by Lumelsky et al. is the Epub date of April 26, 2001, which preceded the journal publication date of May 18 2001.

Lumelsky et al. provides guidance on a population of insulin producing cells derived from human embryonic stem cells (ESCs) (Abstract; pg. 389, col. 1-col. 2). Lumelsky et al. teaches the isolation of clones from human ESCs that expressed insulin in a stable manner (pg. 1390, col. 1-2; pg. 1392, Fig. 4). Further, Lumelsky et al. teaches that the cell population produces insulin in a glucose-dependent manner. A cell that produces a protein, such as insulin, inherently expresses the gene that encodes the protein. Finally, Lumelsky et al. teaches the ectopic subcutaneous engraftment of the insulin producing cells into a mouse with experimental diabetes (pg. 1393, col. 1; Footnote 41). Where the mice had an overall beneficial effect due to

the grafted cells (pg. 1393, col. 2). Thus, by teaching all the limitations of the claims as written, Lumelsky et al. anticipates the instant invention as claimed.

Claims 1, 7, 8, 14, 28, 31, and 34 rejected are rejected under 35 U.S.C. 102(b) as being anticipated by Assady et al. {Assady et al. (September 2000). Vol. 11, Program and Abstract Meeting infor: 33rd Annual meeting of the American Society of Nephrology and the 2000 Renal Week Toronto, Ontario. Canada. Abstract (A1956)}. Applicant should note that the authors are exactly the same as the inventors listed on the instant invention. However, since the date of publication of the abstract by Assady et al. is more than a year before the priority date of 10/15/2001, it is properly applied as 102(b) art.

Assady et al. provides guidance on the generation of stable insulin producing β-cells derived from Human Embryonic stem cells (Abstract). Assady et al. teaches that the β-cells are induced to produce insulin in response to exposure with glucose. A cell that produces a protein, such as insulin, inherently expresses the gene that encodes the protein. Finally, Assady et al. teaches that the cells can be used for cell replacement therapy to treat a patient with a disease such as diabetic nephropathy (Abstract). The use of cells for cell replacement therapy inherently comprises transplanting the cells into a subject. Thus, by teaching all the limitations of the claims as written, Assady et al. anticipates the instant invention as claimed.

Claims 1,2 5, 7-9 12 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Peakman et al. {Peakman et al. (1994) Transplantation 57:384-393}.

Peakman et al. provides guidance on the isolation of insulin producing cells from a human pancreas using collagenase digestion (Abstract; pg. 385, col. 1, Materials and Methods). Further, Peakman et al. teaches the enrichment of a insulin producing cell population by handpicking dithizone-positive islets prior to trypsin and cytospin preparation (pg. 388, col. 2) Peakman et al. teaches that these cell populations are glucose responsive insulin producing cells, which stably secret insulin over a 24 hour period of time (; pg. 385, col. 1, Materials and Methods; pg. 387, pgph 4). "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) Thus, by teaching all the limitations of the claims as written, Peakman et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16, 18-19, 28, 30, 31, 33, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soria et al. {Soria et al. (2000) Diabetes 49:1-6} and in view of Chrenek et al. {Chrenek et al. (1998) Theriogenology 50:659-666}.

Soria et al. provides guidance on derivation of an insulin secreting clone from mouse embryonic stem cells (pg. 1, Abstract, Research Design and Methods). Soria et al. teaches that the insulin secreting clones are selected BY using a neomycin (Neo) selection system, which involves transfection with a Neo construct under the control of the human insulin promoter (pg. 2, Fig. 1, Col. 2, Results). Soria et al. teaches that the ESC derived insulin secreting cells have *in vitro* regulated insulin release (pg. 2, col. 2, pgph 2; pg. 3, Table 1). Further, Soria et al. teaches that the ESC derived insulin secreting cells maintain a stable *in vivo* glucose response after ectopic implantation into the spleen of mice with experimental diabetes (pg. 3, col. 2, pgph 2; pg. 1, Research Design and Methods). Finally, Soria et al. states that xenotransplantation to restore β-cell function in type 1 or 2 diabetes has multiple problems, such as the technical difficulty, risk of animal retroviral infection, and immunological rejection (pg. 1, col. 2, pgph 2). Soria et al. concludes by stating that a useful "alternative is the use of embryonic stem cells" to produce insulin secreting cells (pg. 1, col. 2, pgph 2). Soria et al. does not teach the derivation of insulin producing cells from human embryonic stem cells. Further, Soria et al. does not teach treating the human ESCs with insulin, transferring and selenite.

Chrenek et al. teaches that culture of rabbit embryonic cells in a medium supplemented with insulin, transferring and selenite has a stimulatory effect on cellular development and division rate as compared to control media (pg. 663).

Based on the guidance provided by Soria et al. on the derivation of insulin producing cells from mouse ESCs, it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Soria et al. by using human ESCs as the source of cells to derive insulin producing cells and to supplement the media with insulin,

transferring and selenite, as taught by Chrenek et al. A practitioner in the art would be motivated to derive insulin-producing cells from human ESCs in order to transplant them into humans to treat diabetes and avoid the problems associated with xenotransplantation as taught by Soria et al. The practitioner would be further motivated to supplement the media with insulin, transferring and selenite, as taught by Chrenek et al., in order to increase the number of islet cells produced.

The person of ordinary skill in the art would have a reasonable expectation of success because the substitution of human ESCs for mouse ESCs as the source of cells for the derivation of insulin producing cells comprises a minor modification of the teachings of Soria et al.

Claim 17 is free of the prior art of the record.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy J Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dr. Louis D. Lieto
Patent Examiner
Art Unit 1632

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER